Remarks

Claims 57 and 58 have been added. Support for the new claims can be found in the specification at least at page 5, line 1. Claims 1, 3, 5, 6, 16, 44, 45 and 50-58 are currently pending. No new matter has been added.

Rejection under 35 U.S.C. §112, first paragraph, enablement

Claims 1, 3, 5, 6, 16 and 44-45 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. According to the Examiner, the specification is enabling for a method for treating a subject having an inflammatory joint disorder comprising locally administering to a synovium of the subject an anti-cadherin-11 antibody, provided that applicant provides support as to how to extrapolate data obtained from in vitro assays to the development of effective in vivo human therapeutic methods.

Applicants previously submitted data to demonstrate the enabling nature of the specification as filed. These data were generated by experiments conducted in accordance with the teaching in the specification and thus they establish that the specification was enabling as of the time of filing. The data demonstrate that cadherin-11-Fc fusion protein administered parenterally to mice having serum-induced arthritis caused reduction in clinical symptoms of inflammatory arthritis including reduced ankle thickness, delay in arthritis onset, and decreased maximal arthritic index. The data confirm the teaching in the specification that inhibition of cadherin-11 binding (whether by cadherin-11-Fc fusion protein or anti-cadherin-11 antibody) ameliorates inflammatory arthritis, as shown in a murine arthritis model.

The Examiner however interprets these data as indicative of active immunization with antibody production following administration of the cadherin-11-Fc fusion protein. As discussed during the telephone interview, these experiments do not trigger antibody production in response to the administration of the cadherin-11-Fc fusion protein. This is evidenced by the additional data now submitted in the attached Declaration of co-inventor Dr. Michael B. Brenner. The Declaration data further establishes that systemic administration of cadherin-11-Fc fusion proteins is able to treat experimentally induced rheumatoid arthritis. Therefore, cadherin-11-Fc fusion proteins and anti-cadherin-11 antibodies need not be administered locally for therapeutic benefit.

In addition to the Declaration data, other evidence supports the involvement of passive rather than active immunotherapy as the mechanism of action of the cadherin-11-Fc fusion protein. First, the cadherin-11-Fc fusion protein is structurally analogous to an anti-cadherin-11 antibody. It contains an Fc domain as well as an antigen binding domain. The antigen binding domain of the cadherin-11-Fc fusion protein is a cadherin-11 extracellular domain which is capable of binding to another cadherin-11. The cadherin-11-Fc fusion also possesses two antigen binding domains as does an anti-cadherin-11 antibody. Second, the binding activities of the cadherin-11-Fc fusion protein and the anti-cadherin-11 antibody are similar. Both agents will bind to Fc receptors and to cadherin-11 molecules. Third, the response kinetics in the previously submitted data are consistent with passive but not active immunization. The data show that clinical activity was observed with co-administration of the cadherin-11-Fc fusion protein and arthritis inducing serum. Active immunization would require longer periods of time for therapeutic effect. Fourth, the cadherin-11-Fc fusion proteins administered to the murine subjects were of mouse origin and thus would not be expected to elicit an antibody response. (Applicants wish to point out that the antibody production experiments described in the specification used human cadherin-11 sequences in the fusion protein.)

Taken together, these facts establish that the cadherin-11-Fc fusion proteins do not effect therapeutic benefit via active immunization as suggested by the Examiner. Rather, these agents function similarly to anti-cadherin-11 antibodies and are thus evidence of the therapeutic efficacy of anti-cadherin-11 antibodies in vivo in the treatment of inflammatory joint disease.

In view of the foregoing, Applicants request that the Examiner reconsider and withdraw the rejection.

Respectfully submitted,
Brenner et al., Applicant(s)

By: _____

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